Hypersensitivity pneumonitis

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Current Opinion in Allergy and Clinical Immunology 2010, 10:99–103

Purpose of review

To bring readers up to date on recent reports, both clinical and basic understanding, on hypersensitivity pneumonitis.

Recent findings

Although many antigens and environmental settings have already been described as sources of this hyperimmune pulmonary disease, the literature continues to bring forth other conditions that can cause hypersensitivity pneumonitis. We also highlight new findings in the diagnosis of hypersensitivity pneumonitis, its histopathology, insight into its potential outcomes, and understanding of its immune mechanisms that could lead to new treatments.

Summary

The review will help clinicians in their diagnostic approach to hypersensitivity pneumonitis and lead them to look for other potential sources of the disease. The findings described will help guide further research on the pathophysiology and seek new treatments for this worldwide orphan disease.

Keywords

environment, interstitial lung disease, lung immune response

Curr Opin Allergy Clin Immunol 10:99–103

1528-4050

Introduction

Studies of respiratory symptoms associated with chills fever after exposure to mouldy grain or hay represent the first descriptions of what today is generally known as hypersensitivity pneumonitis or extrinsic allergic alveolitis [1]. Pepys *et al.* [2] coined the term 'farmer's lung' and identified its causative agent, a bacterium found in mouldy foliage. Farmer's lung thus became the term of reference when one talks of hypersensitivity pneumonitis. However, over the years it became obvious that this hyperimmune respiratory disease could be caused by aerosolized antigenic particles found in a large variety of environments. Actually, with modernization of farming practices, farmer's lung has steadily declined and no longer represents most of the cases of hypersensitivity pneumonitis seen around the world. The purpose of this review is to bring the recent findings on hypersensitivity pneumonitis published over the last year and a half. For detailed descriptions of hypersensitivity pneumonitis, its clinical manifestations, its pathophysiology, its treatment and prognosis the reader is referred to a previous publication on the subject [3]. This review is presented under two major sections: clinical and basic science.

Clinical aspects

The section will address novelties in the clinical aspects of hypersensitivity pneumonitis. It is divided into subsections for easier reading.

New environments and causative agents

The list of environments and agents that can cause hypersensitivity pneumonitis is ever increasing. Over the last year a number of case reports describe yet new situations in which hypersensitivity pneumonitis was found. This ever increasing list makes it difficult for clinicians to suspect hypersensitivity pneumonitis in a given patient. The difficulty is even greater considering the case reported by Merget *et al.* [4] when the exposure was indirect via a female partner who was exposed to canaries. In another setting it was found that even lovebirds can cause hypersensitivity pneumonitis [5]. The recommendation that a search for an antigenic source in all cases of interstitial lung disease is very important. Many environmental exposures, often to fungi, can cause interstitial lung disease [6]. Whether this involves hypersensitivity pneumonitis is not certain since some fungal toxin can probably induce interstitial damage by mechanisms other than hypersensitivity pneumonitis. However, fungi in the home can be responsible for classical hypersensitivity pneumonitis. A case of hypersensitivity pneumonitis caused by household exposure to *Cladosporium* spp. was described by Chiba *et al.* [7] and one induced by fungal contamination of hydroponics [8]. Another argument for the role of moulds is the finding that beta-D-glucan, a mould surface antigen, can be retrieved from bronchoalveolar fluid of a case of hypersensitivity pneumonitis caused by moulds [9]. Farmer's lung has taken a very different meaning when the antigen is not in mouldy hay or straw but in moulds in onions and potatoes

[10] or from an enzyme (phytase) added to cattle feed [11]. An interesting observation was reported by Guillot *et al.* [12] who described three cases of hypersensitivity pneumonitis from exposure to dry sausage moulds.

Diagnosis and classification

The clinical presentations of hypersensitivity pneumonitis, especially farmer's lung, are usually reported as acute, subacute or chronic. This classification is questioned by Lacasse *et al.* [13••]. Cluster analysis of a large group of patients who participated in the hypersensitivity pneumonitis study group protocol failed to identify these three categories. The authors suggest a reclassification into two clusters based on disease activity: active vs. sequela. They also argue that the current classification is imprecise and the term subacute is not time-specific as the term should imply.

Pathology and radiological assessment

The pathology and radiological findings of new or acute hypersensitivity pneumonitis usually does present many difficulties. However, in chronic fibrotic hypersensitivity pneumonitis, the differences between the two may be subtle and sometimes the histology cannot differentiate between idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis. An article by Silva *et al.* [14••] suggests that thin section CT can accurately differentiate the two at least 50% of the time. Chronic hypersensitivity pneumonitis is best characterized by lobar areas of attenuation and vascularity, centrilobular nodules and the absence of lower lobe predominance of the involved areas [14••].

Treatment and prognosis

We retrieved no evidence of potential new treatment for hypersensitivity pneumonitis. Avoidance of contact remains the obvious choice. The presence of fibrosis whether on histology or CT scan is now well recognized as a poor prognosis factor [15•]. Two other studies [16,17] have reported acute exacerbation of chronic hypersensitivity pneumonitis without evidence of antigenic contact or increased exposure. Patients at risk of this acute exacerbation are those with fibrotic changes similar to those of IPF with honeycombing. Their exacerbations closely resemble those seen in IPF: poor prognosis and no response to treatment. These observations raise an important question on the cause of these exacerbations, suggesting that the exacerbation may be more related to the presence of lung fibrosis rather than the underlying cause of the fibrosis. The question can be raised if contact avoidance is sufficient to stop the progression once permanent lung damage has developed. Hypersensitivity pneumonitis could present a similar condition to that described in emphysema when the inflammation and continued lung destruction persist even upon cigarette smoking cessation [18]. The hypothesis is supported by the fact that some hypersensitivity pneumonitis patients develop emphysema that is quite similar to that induced by cigarette smoking [19].

Basic science

A hundred years after the initial clinical description of hypersensitivity pneumonitis its pathophysiology still remains unclear. There are controversies in the immune events occurring during the disease. For example, it is not clear if hypersensitivity pneumonitis is an immune complex-mediated or a cellular mediated disease. The former is supported by the presence of high titres of antigen-specific precipitating serum IgG in hypersensitivity pneumonitis patients [20], the latter by combined cell infiltration and granulomas formation [21,22]. Lymphocytes usually account for 60–80% of the broncho alveolar lavage (BAL) recovered cells with a preponderance of $CD8^+$ cells [23,24]. However, the notion that a low $CD4^+$:$CD8^+$ T cells ratio is important in differentiating hypersensitivity pneumonitis from other lymphocytic diseases like sarcoidosis in which this ratio is high may no longer be tenable. Recent studies demonstrated that not all hypersensitivity pneumonitis cases have a low CD4/CD8 ratio [25–27]. Some authors demonstrated that the type of lymphocytes is correlated with the state of the disease: CD8+ cells are associated with the acute phase, whereas CD4+ cells are predominant during the chronic form of hypersensitivity pneumonitis [28–32]. Despite all these contradictory data and focussing on new ideas, recent studies bring, in the last year and a half, new mechanisms susceptible to give a better understanding of the disease.

Is IL-17 a new controversy?

Several groups have supported the critical role of a Th1 immune response in the pathophysiology of hypersensitivity pneumonitis, characterized by the production and release of TNF, IFN-γ, IL-12 and IL-18 by lung cells of patients and mice from hypersensitivity pneumonitis animal models [33,34]. Three recent studies suggest that, in addition to Th1 factors, IL-17 is involved in hypersensitivity pneumonitis [35–37]. Joshi *et al.* as well as Simonian *et al.* demonstrated that Th17 cells and IL-17 are increased in lung of mice exposed to *Saccharopolyspora rectivirgula*, a well known hypersensitivity pneumonitis antigen, compared with control mice [36,37]. Authors showed that genetic deletion or antibody-mediated depletion of IL-17 protects against hypersensitivity pneumonitis by reducing lung inflammation, cells infiltration, cytokines and chemokines production, percentage of $CD11c^+$ cells, and fibrosis due to *S. rectivirgula* exposition. In contrast, another study by Simonian *et al.* found that the expression of IL-17 by γδ and αβ T cells play an important role in eliminating *Bacillus subtilis*-induced hypersensitivity pneumonitis in mice preventing thus lung

tissue damages [35]. IL-17ra$^{-/-}$ mice showed a delayed clearance of the microorganism, increased lung inflammation, collagen deposition, and fibrosis suggesting a regulatory role for these T cells subsets which are poorly understood. However, even if similar observations are obtained with *Nocardia asteroids*, contrasting findings arise with *Cryptococcus neoformans*, *Pneumocystis carinii*, and *Bordetella pertussis* when enhanced clearance of pathogens occurred in the absence of γδ T cells. The divergence of these studies can be explained by the predominant T cell subset expressing Th17 cytokines present in the models. In the *S. rectivirgula*-induced hypersensitivity pneumonitis, CD4$^+$ T cells are the major source of IL-17, whereas γδ T cells are found at a very low numbers. Barrera *et al.* [31] also reported a decrease of γδ T cells in patients with chronic hypersensitivity pneumonitis. In IL-17$^{-/-}$ *S. rectivirgula*-exposed mice, γδ T cells are expanded, whereas CD4$^+$ T cells and macrophages decrease suggesting that γδ T cells reduce lung inflammation and fibrosis by attenuating inflammatory cells infiltration, independently of IL-17. γδ T cells, rather than IL-17, could be an attractive therapeutic target for hypersensitivity pneumonitis.

Although classically classified as a Th1 disease, a Th2 profile could also be involved in the pathogenesis of HP. Barrera *et al.* have evaluated the BAL T cell phenotype and functional profile from healthy control individuals, subacute and chronic hypersensitivity pneumonitis patients. The authors found that T cells from patients with chronic hypersensitivity pneumonitis have lost their effector functions and display a Th2 phenotype with an increase in CXCR4 expression and a decrease in CXCR3 production. Antigen-specific-stimulated cells from BAL of chronic patients showed a higher level of IL-4 in the supernatant and a lower level of IFN-γ production compared to subacute patients. This loss of function and this change of phenotype could be associated with the fibrotic response characterizing the chronic form of the disease [31].

Other cells

Given that hypersensitivity pneumonitis is a complex disease, many cell types, other that T cells, are involved in its pathophysiology. Using the *S. rectivirgula*-induced hypersensitivity pneumonitis mouse model, Nance *et al.* [38] demonstrated that neutrophils are important producers of IFN-γ, a critical factor for granulomas formation. The authors showed that neutrophils recruitment was stopped in the absence of MyD88, probably due to the decreased MIP-2 production, a neutrophils chemokines. These findings suggest that *S. rectivirgula* interacts with a receptor which control MyD88 pathway and the following chemokines and cytokines production. In an in-vitro study, authors reported that *S. rectivirgula* interacts with TLR2 and that cells from TLR2 knockout mice exposed to *S. rectivirgula* showed a decreased MIP-2 production but these mice did not show a decrease in neutrophils numbers.

Since lymphocytes are the major cells in hypersensitivity pneumonitis, the question arises as to what factors trigger their activation, proliferation, and recruitment in lung. Girard *et al.* [39] reported that antigen-presenting CD11c$^+$ cells, which include dendritic cells and macrophages, showed an enhanced maturation profile in a mouse model of hypersensitivity pneumonitis. With this viral-induced exacerbated immune response to *S. rectivirgula* antigen, the authors reported that CD86 and MHC class II maturation markers are enhanced on lung CD11c$^+$ cells from mice infected with Sendai virus and simultaneously exposed to *S. rectivirgula*. Since these mature CD11c$^+$ cells can produce a pro-inflammatory environment and massively activate T cells, these findings could explain, at least in part, the large recruitment of lymphocytes in lung in hypersensitivity pneumonitis.

CD4+CD25+ regulatory T cells have suppressive functions and can down-regulate various autoimmune and inflammatory diseases such as bowel disease and autoimmune diabetes. Park *et al.* [40••] have studied the role of these cells in the regulation of the development of hypersensitivity pneumonitis. In a *S. rectivirgula*-induced murine model of hypersensitivity pneumonitis, the authors have demonstrated that depletion of regulatory T cells results in sicker animals with more pulmonary lesions compared to mice which did not have the depletion. Adoptive transfer of CD4+CD25+ regulatory T cells attenuates *S. rectivirgula*-induced hypersensitivity pneumonitis in CD4+CD25+ regulatory T cell-depleted mice. This attenuation of *S. rectivirgula*-induced hypersensitivity pneumonitis by regulatory T cells seems to be caused by the suppression of interferon-gamma production by CD4 and CD8 T cells and in an IL-10-dependant manner. Taking together, these results may lead to the development of new therapeutics agents for hypersensitivity pneumonitis patients.

BAL findings

BAL is widely used in hypersensitivity pneumonitis diagnosis and to study its pathophysiology. However, the value of BAL is controversial and additional investigations are sometimes needed to differentiate hypersensitivity pneumonitis from other interstitial diseases. Taniuchi *et al.* [41] suggest the usefulness of BAL could be improved by analysing cells content in three different BAL fractions from hypersensitivity pneumonitis patients and control patients. Briefly, the authors studied macrophages, lymphocytes, neutrophils, eosinophils, mast cells, basophils, and Masson bodies (collagen or fibrin covered with epithelial cells) in the recovered fluids from a lavage of 30 ml of saline into a subsegmental lobe of the lung (FBAL-I); a lavage of 50 ml from a more

distal portion of airways (FBAL-II); and finally an additional 50 ml lavage of the alveolar sacs (FBAL-III). In all LBA fractions, a high percentage of lymphocytes was observed (47.5% in FBAL-I; 68.9% in FBAL-III). Lymphocytes from hypersensitivity pneumonitis patients were in an activated form with abundant cytoplasm and some presented cytoplasmic process or nonregular shape. Neutrophils were abundant in FBAL-I fraction (17.4% of recovered cells vs. 2.9% in FBAL-III). Eosinophils and basophils were occasionally found. The authors plan to use this method to compare hypersensitivity pneumonitis with other interstitial diseases to establish a more specific diagnosis with BAL analysis.

Genetic factors

Cytokines and chemokines are important players in the induction of the inflammatory environment in hypersensitivity pneumonitis. Cytokine gene polymorphisms in hypersensitivity pneumonitis have been observed and previous studies related genetic susceptibility to develop the disease to the MHC class II genes and tumor necrosis factor promoter polymorphisms. Mexican hypersensitivity pneumonitis patients have increased frequencies of the alleles Gly-637 and the genotypes Asp-637/Gly-637 and Pro661/Pro661 on the TAP1 (transporters associated with antigen processing 1) gene [42]. The TAP1 gene is associated with the transportation of peptides across the reticulum membrane for the assembly of MHC class I molecules and is located in the MHC class II region. TAP1 is essential for antigen processing and presentation. Polymorphisms in TAP1 gene may lead to exacerbated immune response and interruption of antigen tolerance which may explain why hypersensitivity pneumonitis patients are more susceptible to the disease. Vasakova *et al*. [43] correlated gene polymorphisms with BALF cytokines and chemokines levels in BAL from hypersensitivity pneumonitis patients. They demonstrated that polymorphisms at position -174 and on nucleotide 565 of the IL-6 gene from hypersensitivity pneumonitis patients correlate with a higher BALF ENA-78 (epithelial neutrophils-activating peptide 78) level. This IL-6 gene variation could have a role in ENA-78 regulation in hypersensitivity pneumonitis patients. ENA-78 activates neutrophils, is a potent attractant for these cells, increases extracellular levels of calcium, and promotes exocytosis [43].

Animal models

Animal models are important in the study of complex immune diseases such as hypersensitivity pneumonitis. Usually, animals are exposed to a hypersensitivity pneumonitis causative agent by tracheal instillation, nasal instillation, or inhalation of aerosols. Golec *et al*. [44] have designed an inhalation challenge mimicking natural exposure of mice to the antigenic solution dispersed by ultrasonic nebulizer. This method ensures the penetration of allergen into the deep parts of lungs, alveoli and bronchiole. However, further histopathological studies must be performed [44].

Conclusion

Hypersensitivity pneumonitis being an orphan disease, a limited number of publications on the subject were retrieved. In the past year and a half, new hypersensitivity pneumonitis causative agents have been identified, especially fungi. Indirect exposure through partner has been found to cause hypersensitivity pneumonitis which can complicate the identification of this antigen. New outcomes in hypersensitivity pneumonitis classification and radiological assessments will help clinicians in a less invasive diagnostic approach. Pathophysiological studies brought a better understanding of the disease as well as potential new therapeutic agents for hypersensitivity pneumonitis such as T cells subtypes, and chemokines. Finally, studies of genetics factors also provided additional information of hypersensitivity pneumonitis development.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 161–162).

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